

betaine host-guest complexation with a calixarene receptor: enhanced in vitro anticancer effect

Iten Mamdouh Fawzy, Sherif Ashraf Fahmy, Fortuna Ponte, Emilia Sicilia, Hassan Mohamed El-Said Azzazy

Abstract

p-Sulfonatocalixarenes have shown excellent potential for accommodating chemotherapeutic drugs through host-guest complexation and enhancing their anticancer activity. Betaine has been reported to exert an anticancer effect at high concentrations. In order to increase its concentration in cancer cells, we have complexed it with p-SC4, which releases its content in an acidic environment typical of cancer tissue. In this work, a host-guest complex of the chemically stable, natural, and safe active methyl donor (betaine) and p-sulfonatocalix[4]arenes (p-SC4) was designed and characterized using ^1H NMR, UV, Job's plot analysis, DFT calculations, and molecular modeling for use in cancer therapeutics. The peak amplitude of the prepared host-guest complexes was linearly proportional to the concentration of betaine in the range of $1.0 \times 10^{-7} \text{ M}$ to $2.5 \times 10^{-6} \text{ M}$. The reaction stoichiometry between p-SC4 and betaine in the formed complex was 1:1. The stability constant for the complex is $8.9 \times 10^4 \text{ M}^{-1}$ which corresponds to a complexation free energy of $-6.74 \text{ kcal mol}^{-1}$. Complexation between betaine and p-SC4 was found to involve the insertion of the trimethylammonium group of betaine into the p-SC4 cavity, as supported by the experimental data. The complex displayed enhanced cytotoxic activities against breast adenocarcinoma cells (MCF-7) and cervical cancer cells (HeLa) compared to free betaine. In conclusion, the host-guest complexation of betaine with p-SC4 increases its concentration in cancer cells, which warrants further investigation for cancer therapy.

Royal Society of Chemistry 2021, July